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**UNITED STATES DEPARTMENT OF COMMERCE
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07/969,863 10/30/92 LAWN

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EXAMINER

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18M1

ART UNIT	PAPER NUMBER
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1814

DATE MAILED: 03/29/93

 This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 10-30-92 ☐ This action is made final.

 A shortened statutory period for response to this action is set to expire 3 month(s), — days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

- | | |
|---|--|
| 1. <input checked="" type="checkbox"/> Notice of References Cited by Examiner, PTO-892. | 2. <input checked="" type="checkbox"/> Notice re Patent Drawing, PTO-948. |
| 3. <input type="checkbox"/> Notice of Art Cited by Applicant, PTO-1449. | 4. <input type="checkbox"/> Notice of Informal Patent Application, Form PTO-152. |
| 5. <input type="checkbox"/> Information on How to Effect Drawing Changes, PTO-1474. | 6. <input type="checkbox"/> _____ |

Part II SUMMARY OF ACTION

1. ☒ Claims 4-8 are pending in the application.
Of the above, claims 7 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 4-6 and 8 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☒ This application has been filed with Informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable, ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner, ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved, ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received
☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

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15. Claims 4 and 6 are generic to a plurality of disclosed patentably distinct species comprising (A) substitutions (claims 4, 6, and 7); (B) insertions (claims 4 and 6) and (C) deletions (claims 4-8). These modifications represent changes which have acquired separate status in the art and to have formed a separate subject for inventive effort and a separate field of search since insertions, deletions and substitutions can be used to achieve different ends in the modification of proteins, e.g. the patent of Dull et al refers only to deletion for the elimination of transmembrane regions (see whole patent). Additionally, if species (C) is selection then a further election of preferred deletion between either (C1) deletion of Lys or Arg residues, claim 7, or (C2) deletion of the transmembrane region, claims 5 and 8 is required. Applicant is required under 35 U.S.C. § 121 to elect a single disclosed species, even though this requirement is traversed.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. § 103 of the other invention.

16. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art, restriction for examination purposes as indicated is proper.

17. During a telephone conversation with Daryl Winter on 1-21-93 a provisional election was made with traverse to prosecute the invention of (C2) of species (C), claims 4-6 and 8. Affirmation of this election must be made by applicant in responding to this Office action. Claim 7 is withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention. The substitutions of the generic claims have also been examined.

18. Applicant is advised that the response to this requirement to be complete must include an election of the invention to be examined even though

the requirement be traversed.

19. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

20. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

21. Claims 4-6 and 8 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to the modification by substitution, insertion or deletion of single amino acid residues or deletion of the transmembrane domain. See M.P.E.P. §§ 706.03(n) and 706.03(z).

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of proteins broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and still retain similar activity/utility requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, the problem of predicting protein

structure from mere sequence data of a single protein and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex and well outside the realm of routine experimentation.

5 While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications of other types and the positions within the protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity/utility are limited in any protein and the result
10 of such modifications is unpredictable based on the instant disclosure. One skilled in the art would expect any tolerance to modification shown for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

15 The specification does not support the broad scope of the claims which encompass all modifications and fragments because the specification does not disclose the following : (A) the general tolerance to modification and extent of such tolerance; (B) specific positions and regions of the sequence(s) which can be predictably modified and which regions are critical; (C) what
20 fragments, if any, of the extracellular domain can be made which retain the biological activity of the intact protein; and (D) the specification provide essentially no guidance as to which of the essentially infinite possible choices is likely to be successful.

25 Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed protein in manner reasonably correlated with the scope of the claims broadly including any number of insertions, deletions or substitutions and fragments of any size. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made in the proteins structure and still maintain

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activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and Ex parte Forman, 230 U.S.P.Q. 546 (Bd. Pat. App. & Int. 1986).

22. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 4 and 6 are rejected under 35 U.S.C. § 102(b) as being anticipated by the January 1986 reference Guha et al. The reference of Guha et al discloses partial amino acid sequence data for tissue factor protein (TF) from human brain (see whole publication, especially col. 1, 3rd paragraph of p. 301). This sequence differs in at least one amino acid position from the corresponding part of the sequence of the TF of the instant Figure 2. Thus, the brain TF of Guha et al represents a TF protein where amino acid residues have been at least substituted. While the reference does not disclose the proteins produced by the claimed process, i.e. where the amino acid(s) to be substituted were predetermined by man, the purification or production of a protein by a particular process does not impart novelty or unobviousness to a protein when the same protein is taught by the prior art. See In re Thorpe, 227 USPQ 964 (CAFC 1985); In re Marosi, 218 USPQ 289, 292-293 (CAFC 1983); In re Brown, 173 USPQ 685 (CCPA 1972).

23. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

5 A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

10 Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

15 Claim 4 is rejected under 35 U.S.C. § 103 as being unpatentable over the January 1986 reference of Guha et al in view of the patent of Weissman et al, the patent of Santerre et al and the reference of Pongor. The January 1986 reference of Guha et al discloses partial amino acid sequence data for tissue factor protein (TF) from human brain (see whole publication, especially col. 20 1, 3rd paragraph of p. 301). The reference of Guha et al does not disclose the full cDNA encoding TF and the production of recombinant TF nor does Guha et al disclose making an amino acid substitution in the native sequence.

25 However, the patent of Weissman et al discloses that it is a matter of routine experimentation to obtain the cDNA encoding a desired protein using conventional recombinant techniques with degenerate probes based on knowledge of a short amino acid sequence of as little as 5 continuous amino acids (see whole patent, especially col. 3 and lines 38-56 of col. 3). The patent of Santerre et al discloses various expression vectors and eukaryotic and 30 prokaryotic host cells for the production of a desired protein given a cDNA sequence encoding the desired protein (see whole patent). The reference of Pongor teaches that it is routine experimentation to make single amino acid substitutions in the search for novel mutated protein equivalents (see p. 450, first paragraph).

35 It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to obtain the cDNA encoding TF of human brain using the techniques of Weissman et al and to produce the protein recombinantly in a prokaryotic or eukaryotic host of Santerre et al in order to obtain TF desired in the art in larger quantity than could be obtained from 40 human tissue. It would have then been obvious to routinely modify any predetermined amino acid by substitution using conventional mutagenesis as suggested to one of ordinary skill in the art as suggested by Pongor with the expectation of obtaining novel mutated equivalents of TF.

24. Claim 5 is rejected under 35 U.S.C. § 103 as being unpatentable over January 1986 reference of Guha et al in view of the patent of Weissman et al, the patent of Santerre et al and the reference of Dull et al.

5 The patents of Weissman et al, Santerre et al and Dull et al have been previously discussed. The reference of Guha et al, as previously discussed, does not disclose the full cDNA encoding placenta TF and the production of recombinant TF nor does Guha et al disclose the removal of the transmembrane domain of placenta TF. However, the reference of Guha et al also discloses
10 that purified tissue factor protein (TF) has activity when merely solubilized in TRITON X-100 in the presence of the requisite calcium ions after a purification which removes normally associated lipids (see whole publication, especially col. 1 of p. 299 and the second paragraph of col. 2 of p. 301).

The patent of Dull et al is relied upon to show that it was conventional to determine the transmembrane region of membrane spanning proteins composed
15 of a highly hydrophobic domain of about 20-25 amino acid residues and that exclusion of such a transmembrane domain in when the protein is recombinantly produced results in a soluble form expectedly retaining the activity of the extracellular domain (see whole patent, especially col. 1, lines 36-48).

It would have been prima facie obvious to one of ordinary skill in the
20 art at the time the invention was made to modify the protein obvious to clone over the reference of Guha et al in view of the patent of Weissman et al, the patent of Santerre et al, as discussed above, by determining using conventional techniques, i.e. either by looking at the amino acid sequence or the use of a conventional hydropathy profile of the full amino acid sequence,
25 the location of the transmembrane domain and to delete the transmembrane domain with the reasonable expectation of success in view of the teachings of Dull et al in obtaining an soluble form including the extracellular domain absent the hydrophobic transmembrane domain which does not require detergent solubilization or phospholipids because such characteristic would have been
30 readily apparent as desirable for its ease of use to one of ordinary skill in the art and because Guha et al provide the expectation that insertion into phospholipids was not required for coagulation-inducing activity as long as the protein was adequately solubilized. Alternatively, it would have obvious to produce TF in soluble absent the transmembrane domain for ease of handling
35 when using the protein as an immunogen to raise antibodies to TF, e.g. such as could be used for the detection and/or immunoaffinity purification of the protein.

25. Claim 6 is rejected under 35 U.S.C. § 103 as being unpatentable over

January 1986 reference of Guha et al in view of the reference of Abstract # 1632 of Morrissey et al, the patent of Weissman et al, the patent of Santerre et al and the reference of Pongor. The reference of Guha et al, as previously discussed, also discloses highly resolving affinity techniques for the purification of TF based on its affinity for factor VII (see whole publication) but does not disclose the sequence of TF from human placenta as shown the instant Figure 2 nor substitutions in this protein. However, the reference of Morrissey et al discloses that there is an analogous placenta form of TF which is very similar to the brain TF. The patents of Weissman et al and Santerre et al and the reference of Pongor have been previously discussed.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the purification and sequencing techniques of Guha et al to obtain amino acid sequence data from the human placenta form of TF and to use this amino acid sequence data and/or the similar sequence of the brain TF analog to make probes and screen for the cDNA using convention techniques such as those of Weissman et al and to produce the protein recombinantly in a prokaryotic or eukaryotic host of Santerre et al in order to obtain placenta TF desired in the art in larger quantity than could be obtained from human tissue. It would have then been obvious to routinely modify any predetermined amino acid by substitution using conventional mutagenesis as suggested to one of ordinary skill in the art as suggested by Pongor with the expectation of obtaining novel mutated equivalents of TF, particularly between any amino acids which are non-conserved when the sequences of the human and brain form are compared.

26. Claims 8 is rejected under 35 U.S.C. § 103 as being unpatentable over January 1986 reference of Guha et al in view of the reference of Abstract # 1632 of Morrissey et al, the patent of Weissman et al, the patent of Santerre et al and the reference of Dull et al. The reference of Morrissey et al and the patents of Weissman et al, Santerre et al and Dull et al have been previously discussed. The reference of Guha et al, as previously discussed, does not disclose the full cDNA encoding placenta TF and the production of recombinant TF nor does Guha et al disclose the removal of the transmembrane domain of placenta TF.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the protein obvious to clone over the reference of Guha et al in view of the patent of Weissman et al, the patent of Santerre et al, as discussed above, by determining using

conventional techniques, i.e. either by looking at the amino acid sequence or the use of a hydropathy profile of the full amino acid sequence, the location of the transmembrane domain and to delete the transmembrane domain with the reasonable expectation of success in view of the teachings of Dull et al in obtaining an soluble form including the extracellular domain absent the hydrophobic transmembrane domain which does not require detergent solubilization or phospholipids because such characteristic would have been readily apparent as desirable for its ease of use to one of ordinary skill in the art and because Guha et al provide the expectation that insertion into phospholipids was not required for activity as long as the protein was adequately solubilized. The placenta sequence determined would expectedly inherently correspond to that of instant Figure 2 as would the transmembrane domain determined correspond to about the 20 amino acid stretch of amino acids 221-241. Alternatively, it would have obvious to produce TF in soluble absent the transmembrane domain for ease of handling when using the protein as an immunogen to raise antibodies to TF, e.g. such as could be used for the detection and/or immunoaffinity purification of the protein.

27. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

28. Claims 4-8 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 4 and 6 are indefinite for being in improper Markush format. The Office recommends the use of the phrase "selected from the group consisting of..." with the use of the conjunction "and" rather than "or" in listing the species. See MPEP 706.03(Y).

29. The reference of Edgington et al., having a filing date one month after that of the instant application, discloses the gene for human brain tissue

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factor protein.

30. The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further
5 correspondence regarding this application should be directed to Group Art Unit 1814.

31. Papers relating to this application may be submitted to Group 1810 by facsimile transmission. Papers should be faxed to Group 1810 via the P.T.O.
10 Fax Center located in Crystal Mall 1. The CM1 Fax Center number is (703) 308-4227. Papers may be submitted Monday-Friday between 8:00 am and 4:45 pm (EST). Please note that the faxing of such papers must conform with the Notice published in the Official Gazette, 1096 OG 30, (November 15, 1989).

15 32. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Keith Furman whose telephone number is (703) 308-3453. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

20 March 19, 1993

KEITH C. FURMAN, Ph.D.
PATENT EXAMINER
ART UNIT 1814